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Comparison of Combination Stereotactic Body Radiotherapy Plus High-Intensity Focused Ultrasound Ablation Versus Stereotactic Body Radiotherapy Alone for Massive Hepatocellular Carcinoma

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Background: Thermal high-intensity focused ultrasound ablation is a non-invasive treatment of massive hepatocellular carcinomas. In stereotactic body radiotherapy, ablative radiotherapy is administered to tumors in targeted, limited doses to minimize damage to nearby tissues. We evaluated the outcomes and survival of patients receiving stereotactic body radiotherapy (singular therapy) versus those receiving combination thermal high-intensity focused ultrasound ablation plus stereotactic body radiotherapy (combination therapy).

Material/Methods: We compared data of 160 patients with massive hepatocellular carcinomas (12.5–18 cm) who were treated with combination therapy to those treated with singular therapy between January 2009 and February 2016.

Results: Eighty-four patients were treated with single therapy while 76 were treated with combination therapy. Comparison of short-term outcomes and long-term survival between the groups revealed no significant differences in adverse events. In the combination group, the proportions of patients with complete response, partial response, stable disease, and progressive disease were 52.6%, 21.1%, 21.1%, and 5.3%, respectively; in the single therapy group, the corresponding rates were 0%, 23.8%, 50%, and 26.2%, respectively (P<0.0001). The 1-year, 3-year, and 5-year survival rates in the combination group were 33%, 20%, and 13%, respectively, while those in the single therapy group were 21%, 14%, and 1%, respectively. These data indicated no differences in complications between the groups except for a significantly higher level of skin edema in the combination group (P=0.015).

Conclusions: Combination therapy is more effective than single therapy for the treatment of massive hepatocellular carcinomas, although rates of most complications appear to be similar.

MeSH Keywords: Carcinoma, Hepatocellular • High-Intensity Focused Ultrasound Ablation • Radiotherapy, Adjuvant

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Background

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-associated death worldwide [1,2]. This disease comprises 4 types: nodular, diffuse, massive, and small HCC; massive HCCs (≥10 cm) are the most common [3]. Multiple strategies including single and combination therapies are involved in the treatment of HCCs depending on the size and stage of the lesion. Although hepatectomy is recommended as the first-line choice for HCC treatment, only a small proportion of patients are eligible for resection at the time of diagnosis, particularly since massive HCCs tend to invade major blood vessels (i.e., the portal vein, vena cava, and hepatic artery) [4,5]. Liver transplantation is also limited owing to the lack of appropriate donors. Moreover, patients with massive HCCs usually experience cirrhosis and abnormal liver function, which are also contraindications for surgical intervention [6,7]. Therefore, minimally invasive local procedures such as transhepatic arterial chemotherapy and embolization (TACE), transarterial radioembolization, stereotactic body radiotherapy (SBRT), and local ablative therapy are used to treat patients with massive HCCs [8–10].

Thermal high-intensity focused ultrasound (HIFU) ablation has been used as a non-invasive treatment since the mid-twentieth century [11]. This technique uses focused ultrasound beams that are capable of producing complete coagulative necrosis of the target lesions through intact skin [10]. Thermal HIFU ablation is an emerging non-invasive heat treatment for cancer that has the advantage of avoiding mortality-producing complications and is mainly used as a co-adjuvant therapy in patients with cancer. Some prospective comparison studies have compared thermal HIFU ablation to radiofrequency ablation or TACE for smaller HCCs (<10 cm) [13–15].

SBRT is defined by the Canadian Association of Radiation Oncology as image-guided hypofractionated external beam radiotherapy that can be precisely delivered in single or multiple fractions [16]; this technique has been used to treat intracranial targets since the 1950s [17]. After several decades of enhancements, frameless stereotactic body systems are now generally used to treat tumors, and image-guided radiotherapy ensures the precise targeting of the treatment area [18].

In recent years, many local therapies have been widely used for the treatment of HCCs [8,19]. However, to the best of our knowledge, there have been no studies of thermal HIFU ablation performed in combination with SBRT for massive HCCs. In this study, we evaluated the short-term outcomes and long-term survival of patients receiving SBRT versus those receiving combination thermal HIFU ablation plus SBRT.

Material and Methods

Participants

Between January 2009 and February 2016, 160 patients with massive HCCs (i.e., ≥10 cm) received SBRT alone or in combination with thermal HIFU ablation at the People's Hospital of Zhengzhou (Zhengzhou, China). Investigators obtained informed consent before enrolling participants in clinical trials. This retrospective study was approved by the Ethics Committee of the People's Hospital of Zhengzhou. Eligible patients were those with HCC sizes 10–20 cm; none of the patients received postoperative chemotherapy.

Procedure

SBRT was administered as a first-line therapy. A Gamma Knife (OUR-QGD, China) was used for ablation of the lesion after obtaining the 3-dimensional tumor location using 16-row helical computed tomography (CT). A single radiation dose to the target area was 3 Gy, while the total dose following 15 fractions was 45 Gy. The gross tumor volume was defined as the area of signal abnormality as well as that of any contrast enhancement on magnetic resonance imaging and CT 3-dimensional imaging. An additional 0.3-mm margin was added to account for setup errors to create the planning target volume, 50% of which was covered after delineating an isodose line. After treatment with SBRT for 30 min, thermal HIFU ablation was performed in patients for whom the procedure was feasible for tumor debulking using a recent-model instrument (HIFU-2001, Shanghai Jiao Tong University, China) with ultrasound-guided localization; 200–300 W and an interval of 0.15–0.18 s were used. Each patient underwent thermal HIFU ablation 6 times and received SBRT 15 fractions over the course of treatment. Both procedures were performed 3 times per week. Eighty-four patients with matched tumor characteristics who received only SBRT were included for comparison. To allow for effective penetration of energy when ablating a large tumor, the ultrasound energy was focused on the deep margin of the lesion. The tumor responses to thermal HIFU ablation plus SBRT and to SBRT alone were assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [20].

Follow-up

After the operation, blood tests (including prothrombin time and liver and renal function tests) were routinely performed. Contrast-enhanced CT was performed for assessment every 3 months during the first year and every 6 months thereafter. Details of the patients' conditions and complications, such as arrhythmia and atelectasis, were recorded. Complete ablation was deemed to have been achieved when the enhancement pattern of the lesion was undetectable on imaging 3 months after the ablation procedure.

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Table 1. Patient pretreatment characteristics in the two groups.

	SBRT (n=84)		HIFU+SBRT (n=76)		P value
Age (years) (median with range)	59	(39–82)	58.5	(36–79)	0.706
Male: Female	62: 22		56: 20		0.986
Hepatitis B virus carrier	66	(78.6%)	66	(86.8%)	0.169
Hepatitis C virus carrier	12	(14.3%)	5	(6.6%)	0.114
Presence of comorbidity	47	(56%)	44	(57.9%)	0.804
Cardiac condition	17	(2.0.2%)	8	(10.5%)	0.091
Renal impairment	8	(9.5%)	13	(17.1%)	0.156
Diabetes	14	(16.7%)	8	(10.5%)	0.260
Chronic lung disease	17	(20.2%)	11	(14.5%)	0.338
Ascites					0.958
Absent	60	(71.4%)	54	(71.1%)	
Present	24	(28.6%)	22	(28.9%)	
Child-Pugh grade					0.201
A	63	(75.0%)	50	(65.8%)	
B	21	(25.0%)	26	(34.2%)	
Total bilirubin (μmol/L) (median with range)	22	(8–69)	20.5	(7–73)	0.076
Creatinine (μmol/L) (median with range)	90	(45–201)	89	(44–150)	0.119
Albumin (g/L) (median with range)	36.5	(25–47)	36	(25–46)	0.775
International normalized ratio (median with range)	1.253	(0.8–1.6)	1.25	(0.8–1.6)	0.798
Platelet count $\times 10^9$/L (median with range)	93	(33–371)	87	(33–220)	0.110
Aspartate transaminase (U/L) (median with range)	66	(19–220)	52.5	(18–197)	0.061
Alanine transaminase (U/L) (median with range)	49.5	(13–297)	59.5	(21–241)	0.338
Tumor size (cm) (median with range)	14	(12.5–17)	14.05	(12.5–18.0)	0.571
α-fetoprotein (ng/mL) (median with range)	924.3	(4.54–3050)	785.81	(4.74–3000)	0.218
AJCC staging (2002)					0.563
Stage I	54	(55.3%)	43	(56.6%)	
Stage II	20	(23.8%)	25	(32.9%)	
Stage IIIA	10	(11.9%)	8	(10.5%)	

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA). Significance was defined as a *P*-value <0.05. The Mann-Whitney U test was used to compare continuous variables, while Pearson's chi-squared test was used to compare discrete variables. Survival curves were computed using the Kaplan-Meier method and were compared between groups using the log-rank test.

Results

Characteristics of the patients before treatment

The HIFU ablation plus SBRT group comprised 76 patients with a median age of 58.5 years (range 36–79 years), while the SBRT group comprised 84 patients with a median age of 59 years (range 39–82 years) (Table 1). Hepatitis B virus carriers dominated both groups. Comorbidities were observed in 44 (57.9%) and 47 (56%) of the patients in the combination and SBRT-only groups, respectively (*P*=0.804). There was no

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Table 2. Tumor response rates according to the mRECIST in the two groups.

	HIFU+SBRT (n = 76)	SBRT (n=84)	*P* value
Complete response	40 (52.6%)	0 (0%)	
Partial response	16 (21.1%)	20 (23.8%)	
Stable disease	16 (21.1%)	42 (50%)	
Progressive disease	4 (5.2%)	22 (26.2%)	**0.001***

Table 3. Survival rates of patients with HCC according to the mRECIST in the two groups.

	HIFU+SBRT (n = 76)	SBRT (n=84)	*P* value
1-year survival rate	87 (33%)	50 (21%)	
3-year survival rate	50 (20%)	33(14%)	
5-year survival rate	34 (13%)	2 (1%)	**<0.001***

statistically significant difference in patient pretreatment characteristics between the 2 groups. The median tumor size was 14.05 cm (range 12.5–18 cm) in the thermal HIFU ablation plus SBRT group and 14 cm (range 12.5–17 cm) in the SBRT-only group (P=0.5708). The median serum alpha-fetoprotein (AFP) level was 785.81 ng/mL (range 4.74–3000 ng/mL) in the HIFU ablation plus SBRT group and 924.3 ng/mL (range 4.54–3050 ng/mL) in the SBRT-only group (P=0.170).

Short-term responses

We assessed the therapeutic effect of SBRT alone and HIFU ablation plus SBRT in patients with HCC 3 months after treatments in both groups [19] (Table 2). Forty patients (52.6%) achieved complete ablation after combination treatment. According to the mRECIST, 21.1% of patients achieved partial tumor response, 21.1% had stable disease, and 5.2% had progressive disease. In the SBRT-only group, none of the patients achieved complete tumor response; only 23.8% achieved a partial tumor response, 50% had stable disease, and 26.2% had progressive disease (P<0.0001) (Table 2).

Long-term treatment outcomes

Based on the short-term responses we observed, we further evaluated the long-term outcomes of the 2 therapeutic groups. The 1-year, 3-year, and 5-year survival rates in the thermal HIFU ablation plus SBRT group were 87%, 50%, and 32.3%, respectively, while those in the SBRT-only group were 69.2%, 29.8%, and 2.3%, respectively (P=0.001) (Table 3).

Kaplan-Meier analysis revealed that adding thermal HIFU ablation treatment to SBRT was associated with significantly longer survival outcomes (Figure 1); the median survival times in the

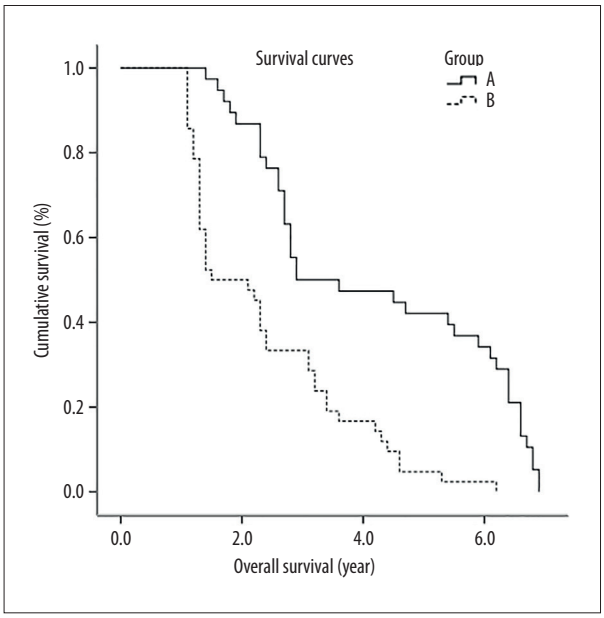

Figure 1. Kaplan-Meier plots of overall survival in the 2 treatment groups. The graph shows the 6-year cumulative survival rate of hepatocellular carcinoma patients who received thermal high-frequency focused ultrasound (HIFU) ablation plus stereotactic body radiotherapy (SBRT) combination therapy (group A) and those who received SBRT alone (group B). The long-term survival of group A patients was longer than that of group B patients.

combination and SBRT-only groups were 2.9 and 1.5 years, respectively (P<0.01). Nine factors were potential contributors to patient survival (Table 4); univariate analysis of these revealed that 3 of them (low level of preoperative serum AFP, combination treatment, and a good response to treatment according to the mRECIST) were predictive of longer survival.

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Table 4. Univariate analysis of overall survival.

	Median survival (years) (SE)		P value
Age (years)			
<57 (n=68)	2.9	(0.258)	
>57 (n=92)	2.3	(0.279)	0.069
Hepatitis B virus infection			
No (n=28)	3.6	(0.688)	
Yes (n=132)	2.4	(0.115)	0.069
Hepatitis C virus infection			
No (n=143)	2.6	(0.149)	
Yes (n=17)	3.4	(0.617)	0.346
Child-Pugh grade			
A (n=134)	2.7	(0.170)	
B (n=26)	2.4	(0.255)	0.722
Ascites			
No (n=138)	2.7	(0.168)	
Yes (n=22)	2.4	(0.467)	0.541
Tumor size (cm)			
≤14.295 (n=86)	2.3	(0.143)	
>14.295 (n=74)	3.1	(0.258)	0.054
α-fetoprotein (ng/mL)			
≤100 (n=89)	3.1	(0.189)	
>100 (n=71)	2.3	(0.126)	0.019*
Treatment			
HIFU+SBRT (n=76)	2.9	(0.926)	
SBRT (n=84)	1.5	(0.229)	0.000*
Response according to the mRECIST			
Complete response (n=40)	5.9	(0.474)	
Partial response (n=36)	3.2	(0.180)	
Stable disease (n=58)	2.2	(0.127)	
Progressive disease (n=26)	1.2	(0.050)	0.000*

Complications

Twenty-eight (36.8%) and 36 (42.9%) of the patients in the combination and SBRT-only groups, respectively, experienced complications (Table 5). Skin edema was the most common complication in the combination group, as it was observed in 11 patients (14.5%). Conversely, only 3 patients (3.6%) experienced skin edema in the SBRT-only group (P=0.015). The most frequent adverse effect in the SBRT-only group was fever (9 patients [10.7%]); in comparison, only 6 patients (7.9%) had fever in the combination group, although the difference was not significant. Other complications such as bruising of the chest wall, third-degree skin burns, and mild bruising of the skin did not significantly differ between the groups.

Discussion

Massive HCC is a common type of primary HCC in which the lesions are ≥10 cm. Thermal HIFU ablation is currently one of the best minimally invasive alternative treatment options for patients with HCCs who are ineligible for curative surgical

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Table 5. Complications occurring after treatment in the two groups.

Complications	HIFU+SBRT (n=76)	SBRT (n=84)	*P* value
Patients with complications	28 (36.8%)	36 (42.9%)	0.438
Patients with two or more complications	6 (7.9%)	7 (8.3%)	0.919
Fever	6 (7.9%)	9 (10.7%)	0.541
Bruising of the chest wall	2 (2.6%)	0	0.433
Third-degree skin burns	3 (3.9%)	0	0.210
Mild bruising over the skin	2 (2.6%)	1 (1.2%)	0.930
Pleural effusion with tapping	8 (10.5%)	1 (2.4%)	0.072
Skin edema	11 (14.5)	3 (3.6%)	**0.015***
Vomiting	1 (1.3%)	2 (2.4%)	1.000
Liver abscess	1 (1.3%)	2 (2.4%)	1.000
Bleeding from esophageal/gastric varices	2 (2.6%)	7 (8.3%)	0.223
Hyperbilirubinemia (>100 μmol/L)	1 (1.3%)	2 (2.4%)	1.000
Acute retention of urine with hematuria	0	1 (1.2%)	1.000
Partial occlusion of thesegmental artery in the left liver lobe	0	1 (1.2%)	1.000

resection. It is critical to improve the quality of life of inoperable patients by reducing pain and prolonging survival time.

SBRT is an attractive treatment option because of its short duration and ability to deliver high ablative doses to the tumor as non-invasive therapy [21]. In SBRT, high doses of photon beam radiation are delivered to the target lesion, causing ionization of water molecules to produce reactive oxygen species, which in turn elicits DNA and cellular damage. Tumor cells are less efficient than normal cells in repairing radiation-induced damage, leading to the preferential destruction of malignant cells [22].

Several studies have demonstrated the favorable therapeutic effects of SBRT in patients with HCCs, as well as good tolerability [23,24]. SBRT produces better therapeutic outcomes when the HCC lesion diameter is <5 cm. In 1995, Blomgren et al. [25] were the first to report 11 patients with primary liver cancers who showed satisfactory outcomes after SBRT treatment. Advancements in SBRT techniques have improved the treatment of HCC tumors with diameters >5 cm as well. Tse et al. [26] used SBRT for the treatment of massive HCCs with a median tumor size of 173 mL (range 9–1913 mL) [27]. All patients had a median survival time of 11.7 months, and none experienced radiation-related liver disease. However, the complete response rate was low [28,29], demonstrating that SBRT alone is not sufficient for patients with massive HCCs, especially as they can develop resistance to radiation that can in turn damage their immune systems. Therefore, more effective treatment options are required for such patients.

Thermal HIFU ablation is a non-invasive hyperthermia-based technology that is used in the treatment of HCCs; it can improve the functioning of the immune system and quality of life of patients while causing minimal adverse effects [30,31]. The energy accumulated at the focused region induces coagulation necrosis of the target lesion by elevating the temperature of the tissue to above 60°C within seconds [32]. It can directly destroy the target tissue and vessels since cell death occurs when exposed to 56°C for >1 s. Recent trials have demonstrated the efficacy and feasibility of thermal HIFU ablation in different clinical applications. Wu et al. [33] reported the safety and efficacy of this technique in large HCCs (mean tumor diameter 8.1 cm; range 4–14 cm); their patients' overall survival rates at 6, 12, and 18 months were 86.1%, 61.5%, and 35.3%, respectively. This indicated that thermal HIFU can be an effective treatment for massive HCCs.

In the present study, thermal HIFU ablation was used after 30 min of SBRT administration. SBRT can damage the vascular endothelium and cause thrombosis and vascular occlusion, which benefits the heat deposition of thermal HIFU and leads to effective treatment. Meanwhile, thermal therapy has an obvious effect in S-phase tumor cell damage, while M-phase cells are sensitive to radiation [34]. After completion of combination treatment, 52.6% of the patients achieved complete ablation, 21.1% had partial tumor response, 21.1% had stable disease, and 5.3% had progressive disease. In contrast, none of the patients in the SBRT group achieved complete tumor response, which was not the case in previous studies [27,28]. The treatment dose in this study was 3 Gy per fraction and the total dose was 45 Gy, while another study on thermal HIFU ablation for

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HCC produced a complete ablation rate of 89.3% [35]. Complete ablation cannot be achieved with thermal HIFU alone, possibly because ultrasound energy cannot pass through the bones of the rib cage that the liver is located behind [36].

Skin complications are a serious adverse event in patients receiving thermal HIFU ablation and SBRT; these include including skin burns and edema. The skin is the first line of defense and absorbs energy easily, especially in the area of the rib cage as some of the energy is deflected by the ribs overlying the tumor, which results in skin damage [36]. The overall complication rate in a previous study on thermal HIFU ablation for HCCs <3 cm was 21.3% [34]. In our study, the overall complication rate was 36.8% in the thermal HIFU ablation plus SBRT group. The reason for our high complication rate may be more attributable to SBRT than to HIFU ablation; however, we are unable to account for the higher complication rate in the SBRT-only group (42.9%), and this will require further investigation. Most of the complications in our study were related to skin edema or skin burns, which may be a consequence of the high-dose energy required for larger tumors. Therefore, the occurrence of skin edema in the combination group was higher than in the SBRT group. There were no differences between the 2 groups in the rates of other complications.

The 1-year survival rate in the HIFU ablation plus SBRT group was 87%, which was higher than that in the SBRT-only group. Therefore, the advantages of combination HIFU ablation and SBRT can be summarized as follows: (1) the complete and partial response rates are higher, and (2) the 1-year, 3-year, and 5-year survival rates are more favorable, as is overall survival. We therefore recommend the use of thermal HIFU ablation plus SBRT as an effective procedure for the treatment of massive HCC. Although some patients in the combination group had incomplete ablation of tumors, patient survival in this group was still better than that in the SBRT-only group. The combination therapy increased the rate of skin edema but not of other complications.

Conclusions

Thermal HIFU ablation is a safe and effective treatment for patients with unresectable HCCs when combined with SBRT; this combination yields better survival outcomes than SBRT alone, making it an attractive therapeutic strategy for massive HCCs. Additional clinical trials are necessary to verify the effect of thermal HIFU ablation in combination with SBRT and to clarify their mechanisms.

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Conflict of interests

None.

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